

## Phenotypic features effectively stratify risk for advanced colorectal neoplasia in asymptomatic adults

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**Background:** While colorectal cancer (CRC) screening is effective and cost-effective for reducing CRC incidence and mortality, it is underutilized (nearly 40% of U.S. adults are either not current with or have never been screened), inefficient (low-risk persons undergo colonoscopy), and costly to the U.S. health care system. A simple and effective way of stratifying risk for advanced neoplasia (AN – CRC and advanced, precancerous polyps) could improve the efficiency and uptake of screening by tailoring colonoscopy toward persons at high-risk and giving low-risk persons less-invasive options. Although several risk factors for AN have been identified, they are not used in clinical practice in part because of inability to integrate the factors to produce a risk estimate.

**Objective:** To derive and validate a risk index for AN (CRC, advanced adenomas, serrated polyps  $\geq 1$  cm) anywhere in the colorectum.

**Methods:** We measured socio-demographic features, medical and family history, lifestyle factors, and physical features in 50-80 year old persons who underwent first-time screening colonoscopy between December 2004 and September 2011, and linked these factors to endoscopic and histologic findings. Using logistic regression, we derived a risk equation on a randomly selected 2/3s of the sample. A 12-variable model was selected based on optimal statistical metrics. Based on model coefficients, we assigned points to each variable to create a risk score, which ranged from -13 to 8. Scores with comparable magnitudes of risk were collapsed into 3 risk categories. The model was tested on the remaining third of the sample.

**Results:** Among 3025 subjects in the derivation set (mean age  $57.3 \pm 6.5$  years; 52% women), the prevalence of AN was 9.4% (including 26 CRCs). Model variables include age, sex, smoking, ethanol use, marital status, NSAID and aspirin use, physical activity, education level, and metabolic syndrome (P-value for fit = 0.09; c-statistic=0.78). Respective risks of AN in the low- (scores of -13 to -5), intermediate- (scores of -4 to 2) and high- (scores of 3 to 12) were 1.52% (95%, 0.07-2.8%), 6.86%, and 26.8% (P-value for trend < 0.001), with respective cohort proportions of 23%, 59% and 18%. Ten low-risk subjects had AN (0 CRCs, 6 distal). Based on finding a distal sentinel polyp, sigmoidoscopy to the descending colon would have detected 7(70%) ANs. Among the 1475 subjects in the test set (mean age  $57.2 \pm 6.5$  years; 52% women), AN prevalence was 8.4%. Risk of AN in the low-risk subgroup was 2.73% (CI, 1.25-5.11%) and was 5.57% and 25.4% in the intermediate- and high-risk subgroups, respectively (P<0.001), with cohort proportions of 23%, 59%, and 18%. Nine low-risk subjects had AN (0 CRCs, 5 distal, 6 detectable by sigmoidoscopy).

**Conclusion:** This new risk index effectively stratifies the risk for AN among asymptomatic adults, identifying a low-risk subgroup of 23% that may be screened effectively and efficiently with tests other than colonoscopy and a high-risk subgroup of 18% in which colonoscopy may be preferable. If validated in other settings, this index could increase both the efficiency and uptake of CRC screening.